PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Pharmacia Case No. 6205.N DV1; MBHB Case No. 03-326-B)

In re Application of:	
Robert B. McCall et al.	Examiner: San Ming R. Hui
Serial No.: 10/078,611	Art Unit: 1617
Filed: February 19, 2002	Confirmation No. 6307
For: METHOD OF TREATING SEXUAL DISTURBANCES	

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

I, MARTIN D. MEGLASSON, declare:

THAT, the attached curriculum vitae (Appendix 1) is accurate which in summary states;

THAT, I received a M.S. degree in Neurophysiology from the University of Houston in 1976;

THAT, I received a Ph.D. degree in Endocrinology from University of Houston in 1981;

THAT, I did post-doctoral work at University of Pennsylvania School of Medicine from 1981-1984;

THAT, I joined The Upjohn Company in 1988 as a research scientist;

THAT, my present position with Pharmacia & Upjohn Company is Director of Pharmacology and my daily duties and responsibilities include supervising a staff of approximately 60 scientists, including more than 12 Ph.D. scientists, that performs research related to central nervous system, cardiovascular system, renal and urinary system, and infectious disease disorders; and planning, performing, analyzing, and preparing for publication research studies related to neuropharmacology, cardiovascular system, and metabolism; and writing and editing documents for submission to national regulatory authorities;

THAT, being so qualified the declarant further states;

THAT, I am a co-inventor of the above-identified patent application;

I. BACKGROUND

This declaration concerns two compounds of claims 8 and 19, PNU-95666 ("95666") and PNU-142774 ("142774"). These compounds should fulfill medical needs for female sexual dysfunction for which there is no existing drug. Specifically, these compounds should represent a useful treatment for forms of female sexual dysfunction such as arousal disorder, orgasmic disorder, and hypoactive sexual desire disorder. Studies of PNU-95666 and PNU-142774 in animal models of sexual desire and motivation indicate that these compounds increase sexual desire, which results in increased motor performance of sexual behaviors (e.g., lordosis in female rats). PNU-142774 is in clinical development for the treatment of sexual dysfunctions in humans. PNU-95666 is in clinical development for the treatment of Parkinson's disease in humans.

II. PRESENT SITUATION

A. "95,666"

THAT, the first compound of claim 19 is (5R)-(methylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2(1H)-one has the internal Pharmacia identifier of PHA-95,666 and is known as "95,666";

THAT, the maleate salt of "95,666" is (5R)-(methylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2(1H)-one (Z)-2-butenedioate (1:1) has the internal Pharmacia identifier of PHA-95,666E and is known as "95,666E";

THAT, "95,666E" has gone thru preclinical testing with success and an IND (Investigational New Drug Application) was filed with the FDA (Federal Food and Drug Administration);

THAT, "95666E" has demonstrated the property of increasing male sexual function in monkeys following oral doses of 0.02 mg/kg and 0.05 mg/kg (Table 1).

Table 1. Behavioral events by male rhesus monkeys when visually exposed to estrogen-primed female rhesus monkeys. The data[1] are shown as the median number of scoring periods when the behavior was displayed during the 4-hour period after oral dosing with placebo or "95666E". N=4 monkeys/group.

Oral Dose (mg/kg)	**"95666E"**	
	Rigid Penile Erections	**Masturbation**
Placebo	0	0
0.02	12	6
0.05	6	25

THAT, "95666E" has demonstrated the property of ameliorating sexual dysfunction in female rats following oral doses of 0.05 mg/kg (Table 2). In this experiment the test subjects had been ovariectomized and then partially repleted with estrogen by injecting 150-200 micrograms of estrone s.c. This dose of estrone was found to produce minimal lordotic responses in a majority of animals tested. Thus, the test animals can be said to exhibit a form of sexual dysfunction when studied in the absence of PNU-95666.

[1] The experiments were performed following the procedure disclosed in *Pharmac. Biochem. Behav.* 35, 659-664 (1990), with the modification that the test substance was administered orally.

Table 2. Frequency of lordotic responses by female rates in response to mounting by a male rat two hours after an oral dose[2].

Treatment	**Frequency of Lordotic Responses to Male Mounting**		**Signed Rank Test for Increased Frequency of Lordosis with PNU-95666**
	Mean ± S.E.M. (N)	**Median**	
Placebo	0.137 ± 0.041 (33)	0.00	--
PNU-95666 0.05 mg/kg P.O.	0.243 ± 0.050 (33)	0.133	P=0.05

THAT, phase I clinical trials with "95,666E" were successfully conducted without problems of toxicity. Healthy adult men and women tolerated a single oral dose of 0.1-5 mg without exhibiting signs of clinical intolerance. At an oral dose of 10 mg, healthy adult men and women exhibits signs that constituted intolerance for the single dose. These included dizziness, pallor, and syncope (symptoms related to the cardiovascular side effects of dopamine agonists) and nausea (a symptom related to the pro-emetic side effect of dopamine agonists). These data indicate that healthy adult men and women tolerate PNU-95666E at a dose of 5 mg, but not at a dose of 10 mg or greater. These data define the operative range for a single oral dose of PNU-95666E as being less than 10 mg and most desirably 5 mg or less to assure patient comfort and safety;

THAT, phase I clinical trials with "95,666E" were successfully conducted in men with moderate to severe organic erectile dysfunction (ED). The relevant result of those studies are that an oral dose of 1, 2, 4, or 6 mg of PNU-95666E was tolerated by patients with ED. An oral dose of 8 mg of PNU-95666E was poorly tolerated with side effects of mild to moderate intensity being observed (e.g., dizziness and nausea). One patient who received an 8 mg dose developed shock and required hospitalization. These data define the operative range for a single oral dose of PNU-95666E as being less than 8 mg and most desirably 6 mg or less to assure patient comfort and safety.

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[2] The experiments were performed following the procedure disclosed in Psychopharmacology 91, 96-100 (1987).

THAT, phase II studies were conducted with "95,666E" for treating Parkinson's Disease. The relevant result of those studies are that men and women with moderate to advanced Parkinson's Disease who were receiving levodopa therapy tolerated oral PNU-95666E at doses of 0.5 mg, 2 mg, or 6 mg administered 4 times daily for 35 days. A dose-escalation drug design was used such that patients were initially treated with 0.25 mg (administered four times daily) for 5 days, then 0.5 mg (administered four times daily) for 5 days, then 1 mg (administered four times daily) for 5 day, then 2 mg (administered four times daily) for 5 days, then 4 mg (administered four times daily) for 5 days, then 6 mg (administered four times daily) for 5 days.

THAT, phase II studies were conducted with "95,666E" for treating Erectile Dysfunction (ED). The relevant result of those studies are that men with mild to moderate ED who were given a 3 mg oral dose of PNU-95666E showed improved erectile function as measured using an Ambulatory Rigidity and Tumescence Monitoring system.

THAT, phase II studies were conducted with "95,666E" for treating Erectile Dysfunction (ED). Men with mild to moderate erectile dysfunction received capsules containing 3 mg of PNU-95666E and were given instructions to take a maximum of 1 capsule every 48 hours. Compared to patient responses on the International Index of Erectile Function (IIEF) prior to drug treatment, 61% of patients in the PNU-95666E group reported improved sexual functioning, a statistically significant treatment effect. Sixty-nine percent of patients reported increased intercourse satisfaction. Patients also reported increases in the IIEF domains related to orgasmic function, sexual desire, and overall satisfaction. PNU-95666E was generally well tolerated as indicated by a 6.6% drop-out rate for patients receiving PNU-95666E during the 4 week trials;

THAT, IN SUMMARY, the foregoing data indicate that PNU-95666E is safe for administration to humans when given orally at doses of 5-6 mg or less. When administered to patients with one form of sexual dysfunction, male erectile dysfunction, PNU-95666E is effective in improving sexual function when administered at an oral dose of 3 mg. These data indicate that the operative range for PNU-95666E in treating sexual dysfunction is a dose of 5-6 mg or less. A dose of 3 mg demonstrates the desired a combination of safety and efficacy. It is possible that the same combination of safety and efficacy could be achieved at doses greater than 3 mg, but

(..continued)

less than or equal to 5-6 mg. It is also possible that a dose less than 3 mg could demonstrate efficacy and also be safe;

B. "142,774"

THAT, the second compound of claim 8 is, (5R)-5-(methylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-2(1H)-thione which has the internal Pharmacia identifier of PHA-142,774 and is known as "142,774";

THAT, the maleate salt of "142,774" is (5R)-5-(methylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-2(1H)-thione malate which has the internal Pharmacia identifier of PHA-142,774E and is known as "142,774E";

THAT, "142,774E" has gone thru preclinical testing with success and an IND was filed with the FDA;

THAT, "142774E" has demonstrated the property of increasing male sexual function in monkeys following oral doses of 0.02 mg/kg and 0.05 mg/kg (Table 3).

Table 3. Behavioral events by male rhesus monkeys when visually exposed to estrogen-primed female rhesus monkeys. The data[3] are shown as the median number of scoring periods when the behavior was displayed during the 4-hour period after oral dosing with placebo or "142774E". N=4 monkeys/group.

Oral Dose (mg/kg)	**"142774E"**	
	Rigid Penile Erections	**Masturbation**
Placebo	0	0
0.02	17	16
0.05	28	30
0.125	5	4

THAT, "142774E" is similar to "95666E" based on its stimulation of male sexual behavior at the oral doses at which it is most effective, that is 0.02 and 0.05 mg/kg (compare Table 1 and Table 2). Although this is a matter of theory, the somewhat greater stimulation of sexual behavior by "142774" may be based on small differences in the pharmacokinetic or tissue distribution properties of the compounds.

THAT, "142774E" is most effective in stimulating male sexual behavior when administered orally at 0.02 or 0.05 mg/kg. By comparison, administration of a higher oral dose of 0.125 mg/kg produces a level of sexual behavior that is markedly less than 0.05 mg/kg and, indeed, is not statistically different from administration of placebo. Thus, administration of an optimal dose is necessary to elicit stimulation of sexual behavior and this oral dose is 0.05 mg/kg or greater, but less than 0.125 mg/kg.

THAT, "142774E" has demonstrated the property of ameliorating sexual dysfunction in female rats following oral doses of 0.05 mg/kg (Table 4). In this experiment the test subjects had been ovariectomized and then partially repleted with estrogen by injecting 150-200 micrograms of estrone s.c. This dose of estrone was found to produce minimal lordotic responses in a majority of

[3] The experiments were performed following the procedure disclosed in *Pharmac. Biochem. Behav.* 35, 659-664 (1990), with the modification that the test substance was administered orally.

animals tested. Thus, the test animals can be said to exhibit a form of sexual dysfunction when studied in the absence of PNU-95666.

Table 4. Frequency of lordotic responses by female rates in response to mounting by a male rat fifteen minutes and two hours after an oral dose[4].

Treatment	**Frequency of Lordotic Responses to Male Mounting**		**t-Test for Increased Frequency of Lordosis with PNU-142774**
	Mean ± S.E.M. (N)	**Median**	
15 minutes after oral dose			
Placebo	0.109 ± 0.042 (19)	0.00	--
PNU-142774 0.05 mg/kg P.O.	0.373 ± 0.0850 (33)	0.333	P=0.01
2 hours after oral dose			
Placebo	0.225 ± 0.088 (15)	0.091	--
PNU-142774 0.05 mg/kg P.O.	0.633 ± 0.111 (15)	0.800	P=0.004

THAT, "142774E" has demonstrated the property of ameliorating sexual dysfunction in female rats in a dose-dependent manner (Table 5).

THAT, "142774E" is most effective in stimulating female sexual behavior when administered orally at 0.02 or 0.05 mg/kg. By comparison, administration of a higher oral dose of 0.125 mg/kg produces a level of sexual behavior that is markedly less than 0.05 mg/kg and, indeed, is not meaningfully different from administration of placebo. Thus, administration of an optimal dose is necessary to elicit stimulation of sexual behavior and this oral dose is 0.05 mg/kg or greater, but less than 0.125 mg/kg.

[4] The experiments were performed following the procedure disclosed in Psychopharmacology 91, 96-100 (1987).

Table 5. Dose-response for increased frequency of lordotic responses by female rates in response to mounting by a male rat two hours after an oral dose[5].

Oral Dose of PNU-142774 (mg/kg P.O.)	0	0.020	0.050	0.125
Frequency of Lordotic Responses Mean ± S.E.M. (N)	0.14 ± 0.05 (17)	0.21 ± 0.11 (12)	0.36 ± 0.10 (18)	0.17 ± 0.08 (10)

THAT, phase I single-dose clinical trials with "142,774E" were successfully conducted without problems of toxicity. Healthy adult men and women tolerated a single oral dose of 0.2-2 mg without exhibiting signs of clinical intolerance. At an oral dose of 4 mg, healthy adult men and women exhibits signs that constituted intolerance for the single dose. These included postural hypotension, a symptom related to the cardiovascular effects of dopamine. These data indicate that healthy adult men and women tolerate PNU-142774E at a dose of 2 mg, but not at a dose of 4 mg or greater. These data define the operative range for a single oral dose of PNU-142774E as being less than 4 mg and most desirably 2 mg or less to assure patient comfort and safety. Determination of the plasma concentrations of PNU-142774 in normal volunteers who received 1 or 2 mg oral doses indicated that their drug levels equaled or exceeded the plasma PNU-142774 concentrations that are known to produce stimulation of sexual behavior in male monkeys and female rats;

THAT, phase I multiple-dose clinical trials with "142,774E" were successfully conducted without problems of toxicity. Healthy adult men and women tolerated a daily oral doses of 0.2-2 mg without exhibiting signs of clinical intolerance. These data indicate that healthy men and women tolerate "142,774E" at a dose of 2 mg or less when administered once daily.

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[5] The experiments were performed following the procedure disclosed in Psychopharmacology 91, 96-100 (1987).

THAT, phase II clinical trials with "142,774E" were successfully conducted without problems of toxicity. Healthy adult women and women with sexual arousal and/or orgasmic disorder took 1 mg of "142,774E" as needed prior to engaging in sexual activity. The response to "142,774E" or placebo is shown in Table 6. These data indicate that a dose of 1 mg of "142774E" improves orgasmic function in both healthy women and women exhibiting sexual dysfunction when administered as needed, but no more frequently than once per day.

Table 6. Female Sexual Function Index Orgasmic Domain Score (Journal of Sexual and Marital Therapy 2000; 26:191-208). Data are shown as mean response.

	Placebo	**"142,774E"**
Healthy Women	0	0.24
Female Sexual Dysfunction Patients (Arousal and Orgasmic Disorders)	1.1	1.3

THAT, phase II clinical trials with "142,774E" were successfully conducted without problems of toxicity. Adult women with hypoactive sexual desire disorder took 1 mg of "142,774E" once daily for seven days and then twice daily for 3 months. The response to "142,774E" or placebo is shown in Table 7. These data indicate that women exhibiting sexual dysfunction show improved orgasmic function at a dose of 1 mg of "142774E" when administered once or twice daily. Women tolerated 1 mg of "142,774E" when administered once daily without signs of intolerance. When 1 mg of "142,774E" was administered twice daily, one patient exhibited symptoms of falling blood pressure, a symptom related to the cardiovascular effects of dopamine. These data indicate that a dose of 1 mg of "142774E" improves orgasmic function in women exhibiting sexual dysfunction when administered once or twice per day. Furthermore, these data indicate that a dose of 1 mg of "142774E" is tolerated when administered once per day, whereas a dose of 1 mg of "142,774E" is not tolerated when administered twice daily. These data demonstrate that the operative range for treating female sexual dysfunction is a dose of 1 mg of "142774E" administered once daily, but no more frequently.

Table 7. Female Sexual Function Index Orgasmic Domain Score (Journal of Sexual and Marital Therapy 2000; 26:191-208). Data are shown as mean response.

	Placebo **N = 82 subjects**	**"142,774E"** **N=92 subjects**
Female Sexual Dysfunction Patients (Hypoactive Sexual Desire Disorder)	0.5	0.9

III. US Patent 5,273,975 (MOON)

THAT, I am aware of US Patent 5,273,975 (MOON) and its relevant contents;

THAT, MOON generically discloses the two compounds of claims 8 and 19, but neither is specifically exemplified;

THAT, I am aware that MOON discloses (column 2 at lines 19-23):

> In addition, central 5-HT receptor activation are believed to be involved in mediating sexual behavior. These compounds would be useful to stimulate sexual activity and to alleviate impotence.

THAT, I am also aware that MOON discloses (column 9 at lines 40-45):

> In the hypothermia and hypoxic stress tests, compounds of the invention have been found more potent then related compounds, showing ED50's values as low as 0.05 mg/kg. The compounds also had good activity in the hypothermia test when the animals were dosed orally with the drug.

THAT, I am further aware that MOON teaches that the compounds of MOON should be used in a dosage range of 10 mg to 1,200 mg (column 9, lines 58-65);

THAT, the available evidence from the human clinical trials with "95,666E", which I discussed above, indicates that:

(1) the dosage range of about 8 mg/day to about 48 mg/day (administered orally in two equal doses per day) which is within the disclosure of MOON *is* operable for treating Parkinson's Disease but is NOT operable for treating sexual dysfunction,

(2) clinical trials in normal volunteers and patients with sexual dysfunction with the compounds of claims 8 and 19 have shown:

(a) the two compounds of claims 8 and 19 are not tolerated above 5-6 mg because of orthostatic hypotension, vomiting, nausea and dizziness.

(b) the two compounds of claims 8 and 19 would not be useful at 10 mg and above;

THAT, as I have stated above:

(a) "95,666E" is being used to treat Parkinson's disease at doses of 8 mg/day to 48 mg/day and

(b) the two compounds of claims 8 and 19 are not tolerated by normal volunteers or patients with erectile dysfunction above 5-6 mg because of orthostatic hypotension, vomiting, nausea and dizziness and

(c) that these two compounds would not be useful at 10 mg and above. These seemingly inconsistent statements are not inconsistent for the following reasons.

(1) When treating Parkinson's disease "95,666E" is given in repeated small (sub-therapeutic) doses each day and the dose level slowly escalated into the effective dose range of 8-48 mg/day over a period of many days. By this procedure the side effects (toxicity) disappear. The mechanism for disappearance of the side effect has been speculated to involve desensitization of D2 receptors on sympathetic autonomic neurons. Desensitization is a common, probably universal, response by G-protein coupled receptors to sustained exposure to agonists (such as "95666" and "142774"). A practical implication of the well-known desensitization of G-protein coupled receptors by agonists is that frequent, repeated doses of "95666" or "142774" (such that near constant drug exposure occurs) would be expected to render these compounds inactive for treating sexual dysfunction as a result of receptor desensitization.

(2) Parkinson's Disease and Sexual Dysfunction patients are different in respect to the morphology and function of their autonomic nervous systems and, therefore, the doses of "95666" and "142774" tolerated by these patients will be different. Parkinson's Disease patients have dysautonomia (abnormally deficient functioning of the autonomic

nerves), which is not normally present in normal healthy volunteers or patients with sexual dysfunction. Thus, the mechanism of progressive development of tolerance to high doses of "95,666E" or "142774" many occur particularly in Parkinson's Disease patients.

(3) Irrespective of the mechanism of progressive tolerance in Parkinson's Disease patients and whether the mechanism is specific to Parkinson's Disease or more widely applicable, in the claimed method the pharmaceutical agent is not taken in multiple daily doses, but rather on an intermittent basis (for example, once per day or more likely less frequently) according to the patient's desire for sexual intercourse and medical advice. At present, medical advice is that "95,666E" or "142774" not be taken more often than once per 48 hours. With infrequent administration of this type, progressive tolerance to the action of agonists, such as "95666" and "142774", is unlikely to occur and would not be predicted from any currently available results with the compound. Thus, administering doses higher than 5-6 mg of the compounds in claims 8 and 19 would evoke unacceptable discomfort and be unsafe to sexual dysfunction patients; and administering doses more frequently than once daily would likely produce no benefit for treating sexual dysfunction.

THAT, therefore, if one tested the compounds of claims 8 and 19 for sexual dysfunction in the dosage range taught by MOON, the evidence indicates:

(1) there is NO UTILITY FOR THE CLAIMED PURPOSE and

(2) there is TOO MUCH TOXICITY;

THAT, given the teaching of MOON about the dosage range, it is surprising and unexpected to me that the compounds of claims 8 and 19 should be useful for treating sexual dysfunction in doses of 5-6 mg or less as indicated by human clinical trials and non-human animal experiments;

A. Further Evidence Of A Narrow Dose Range

THAT, further, of the operable dosage range being very narrow comes from the fact that dopamine compounds such as those of claims 8 and 19 have a narrow bell shaped curve for producing sexually enhancing effects. This supports the fact that an optimum dose of 2-5 mg means no activity at about 10 mg;

THAT, when an oral dose of "142774E" is administered to male monkeys at 0.02 or 0.050 mg/kg penile erections and masturbatory behavior is increased compared to placebo. When an higher oral dose of "142774E" (0.125 mg/kg) is given to male monkeys, sexual behavior is reduced compared to a lower dose of the drug and only slightly greater than placebo (refer to Table 3). Furthermore, when an oral dose of "142774E" is administered to female rats at 0.02 or 0.05 mg/kg sexual receptivity is increased, as indicated by the frequency of lordotic responses (refer to Table 5). When an higher oral dose of "142774E" (0.125 mg/kg) is given to female rates, sexual receptivity is reduced compared to a lower dose of the drug and only slightly greater than placebo (refer to Table 5). In other words, "142774E" become less effective at producing the desired sexual response when the dose is increased above an optimum dose of about 0.05 mg/kg (which produces a plasma drug concentration of about 1-2 ng/ml). The optimum dose in the monkey or rat is equivalent to an oral dose of 3-4 mg administered to an adult human on a dose basis. When plasma drug concentrations are compared, the optimum dose in the monkey or rat is equivalent to a dose of 1-2 mg administered to an adult human;

B. Additional Evidence of A Narrow Dose Range

THAT, additional evidence of a very steep dose response curve for the compounds of claims 8 and 19 is exemplified in the Phase I tolerance studies in normal, healthy human volunteers. For example, at a 5 mg dose of "95666E" no subjects exhibited syncope (fainting as a result of transient cardiovascular collapse); at a dose of 10 mg 2-of-8 subjects exhibited syncope. In the Phase I tolerance studies in men with Erectile Dysfunction, 1-of-32 patients receiving a dose of 6 mg or less exhibited a moderate adverse event. In the same study, 4-of-8 patients receiving a dose of 8 mg had a moderate or severe adverse event. Pharmacokinetic studies with "95666E" indicate that plasma concentrations of the drug are proportional to the dose administered. This indicates that the explanation for the sharply rising dose-response relationship for adverse effects with "95666E" is not due to unexpectedly large differences in the concentration of drug in the plasma with higher

doses. As a result, dose-response relationships for the desirable and undesirable pharmacological effects of "95666" and "142774" must be established with precision for these agents to be used in a therapeutic manner to treat sexual dysfunction with safety.

(C) Apparent Discrepancy Between "10 mg to 1,200" mg And "0.05 mg/kg"

THAT, with regard to the "dose" of the compounds of US Patent 5,273,975 (MOON), MOON discloses the following:

> (1) "The compounds listed below were tested and found to have possible useful antipsychotic activity properties as indicated by their having CNS activity (ED_{50} numbers of less than 50 mg/kg values) in the known hypothermia and/or hypoxic stress tests;" (column 9, lines 3-7)
>
> (2) "Doses of the compound under study began at 100 mg/kg and were decreased at a 0.3 log interval until no responders were obtained." (column 9, lines 11-14)
>
> (3) In the hypothermia and hypoxic stress tests, compounds of the invention have been found more potent than related compounds, showing $ED_{50's}$ values as low as 0.05 mg/kg. (column 9, lines 40-43)
>
> (4) That the compounds were dosed intraperitoneally (ip) or subcutaneously (sc) when tested in mice (column 9, lines 9-11).
>
> (5) That "the compounds also had good activity in the hypothermia test when the animals were dosed orally with the drug" (column 9, lines 43-45).
>
> (6) That with respect to dosing in humans for the purpose of producing therapeutically beneficial effects "Initial dosages of the compounds of the invention are ordinarily in the area of at least 10 mg up to about 1200 mg per day orally;" (column 9, lines 59-60)

THAT, while statements (1), (2), (3), (4), and (5) and (6) appear to be in conflict, they are NOT in conflict;

THAT, statements (1), (2), (3), and (4) relate to *parenteral* administration;

THAT, statements (5) and (6) relate to *oral* administration;

THAT, the statements are NOT in conflict because they related to different things, statements (1), (2), (3), and (4) relate to *parenteral* administration and statements (5) and (6) relate to *oral* administration

THAT, it is my opinion that statements (1), (2), (3), and (4) are correct with respect to teaching that the compounds of the invention likely possess antipsychotic, and statement (5) is correct with respect to the principle that the compounds can be administered orally, but the foregoing statements are irrelevant to statement (6), which relates to the effective dosage when administered by the preferred oral route. Furthermore, statements (1), (2), (3), and (4) do not teach the therapeutic oral dosage of compounds of the invention because these statements relate solely to parenteral drug administration. Statement (5) does not teach the therapeutic oral dosage since it does not describe an effective oral dose and it is well known to those of ordinary skill in the art that the effective oral dose cannot be predicted solely from the effective parenteral dose because of the large variation in absolute oral bioavailability for different compounds, including compounds of apparently similar chemical structures. An example in support of this statement is the following; the absolute oral bioavailability of "95666" in rats is approximately 34%; by comparison, the absolute oral bioavailability of "142774" in rats is approximately 70%. This large difference in absolute oral bioavailability would not be expected and, therefore, could not be anticipated from the difference in chemical structure or the potency of the compounds upon parenteral administration. Statement (6) teaches that the therapeutically effective oral dose is 10 mg or greater, but less than 1200 mg when administered to humans. By making the ordinary assumption that a typical adult human weighs 70 kg, it can be calculated that the effective oral dose taught by MOON is 0.14 mg/kg or greater, but less than 17.14 mg/kg.

THAT, since both Dr. Moon and myself were both employed by the assignee of MOON at the time of the invention, I had access to the records and data which I checked before making this Declaration;

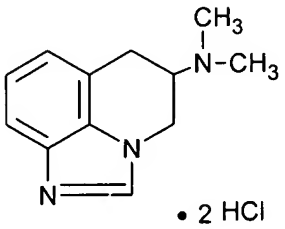
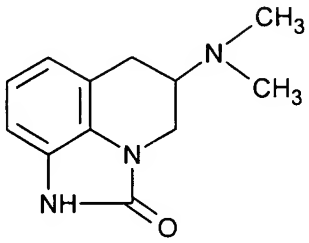
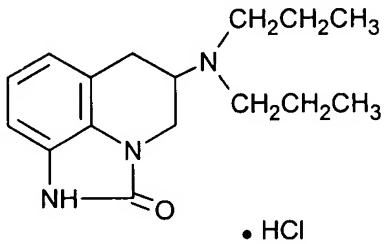
THAT, I have discussed the conflict with Dr. Moon;

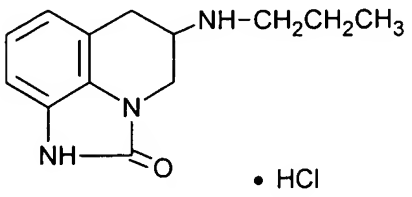
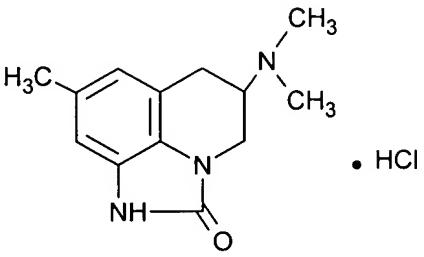
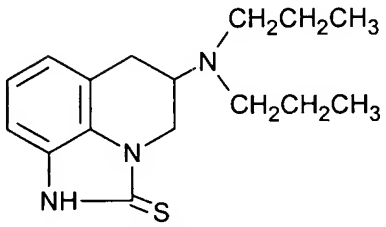
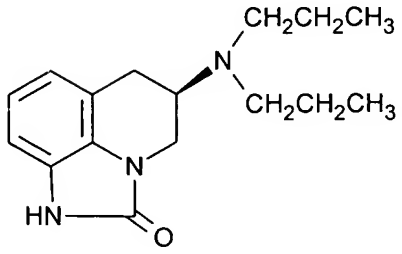
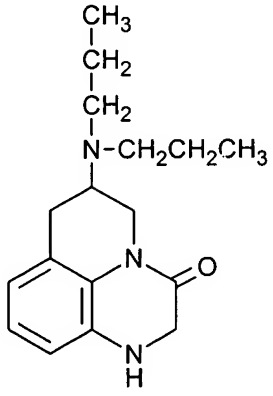
THAT, the reasons for my opinion that statement (6) teaches the effective oral dosage range for the compounds of the invention and that statements (1), (2), (3), (4), and (5) are irrelevant to teaching the oral dosage range both to the inventors at the time the invention was made and to those of ordinary skill in the art are as follows. It would be clear to one of ordinary skill in the art that drug absorption will not be greater after oral dosing than after intraperitoneal or subcutaneous dosing and in most cases will be less. This well known finding is due to incomplete drug absorption in the intestine or the metabolism of the drug substance to inactive

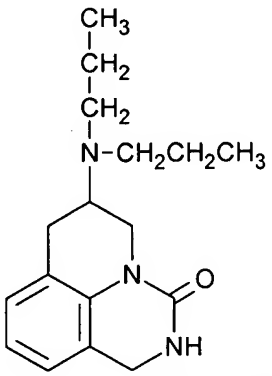
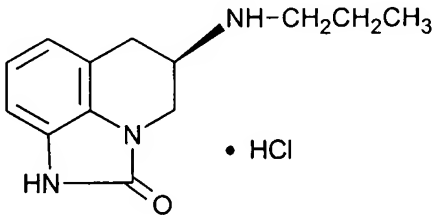
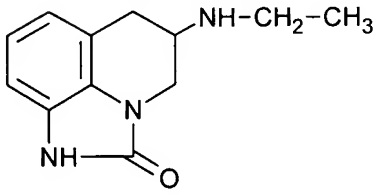
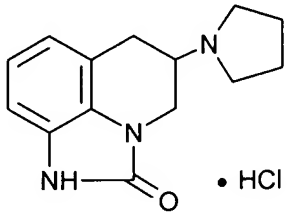
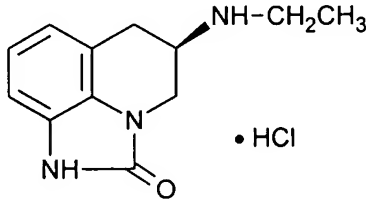
forms prior to its egress from the hepatic circulation. Thus the dosage that would be administered orally to produce therapeutic benefit would have to exceed the minimum effective parenteral dosage in most cases. It would be clear to one skilled in the art that the inventors made this common assumption of incomplete oral absorption described above when specifying that dosages "of at least 10 mg" (>0.14 mg/kg in typical 70 kg human patient) for therapeutically effective oral treatment in the face of statement (3).

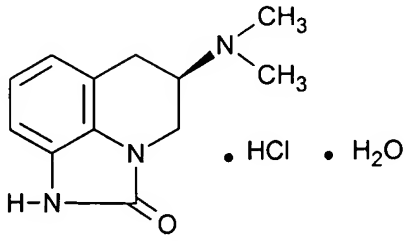
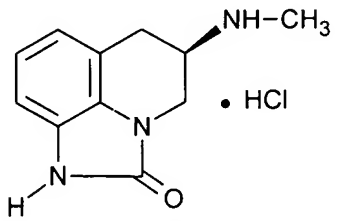
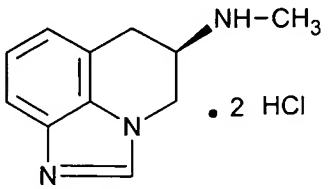
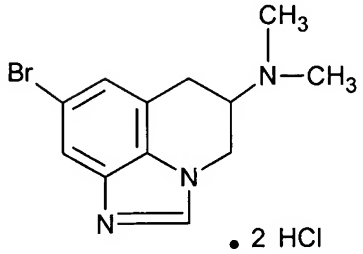
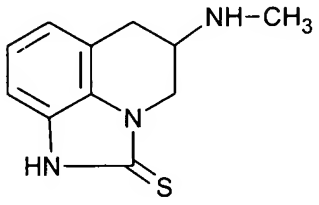
THAT, in support of my position that the ED_{50} mg/kg statements (1) and (3) above relate to parenteral and not oral administration, I have gone back in the original research notebook (#20859-MFP) and located the ED_{50} parenteral and oral data for compounds within the scope of MOON. The ED_{50} parenteral data for the compounds of MOON, support statements (1) and (3) as written by the inventors. The oral ED_{50} data is set forth below in Table 4. It is noteworthy that the oral ED_{50} data do not demonstrate a single example of activity at a dose as low as or near to 0.05 mg/kg; however, effective oral doses of 0.23 mg/kg and greater are exemplified.

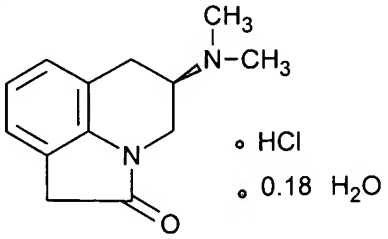
Table 4. Hypothermia Assay results after oral administration for compounds of the invention that were evaluated orally. The hypothermia assay was performed as described in MOON (column 9, lines 8-17) except that reference to the original laboratory records indicates oral administration was performed. Data are expressed as an oral ED_{50} (ED_{50} as defined by MOON). The range of observed oral ED_{50} values for the evaluated compounds of the invention is from 0.23 mg/kg to greater than 30 mg/kg.

Test Substance	Oral ED_{50} (mg/kg)
PNU-77042E  • 2 HCl	1.3
PNU-77564  racemate	3.1
PNU-77566A  • HCl	0.73

PNU-77567A 	1.3
PNU-79291A 	>30
PNU-86169 	1.7
PNU-86170  (R)-enantiomer	0.55
PNU-86173 	0.73

PNU-86264 	9.7
PNU-91356A  (R)-enantiomer	0.41
PNU-91412 	1.3
PNU-92607E 	5.5
PNU-93457A  (R) isomer	0.23

PNU-95512E 	1.3
PNU-95666A 	0.41
PNU-95667E 	0.73
PNU-97393E 	>30 ~30 (results of 2 independent assays)
PNU-98507 	2.3

PNU-98931E  ∘ HCl ∘ 0.18 H_2O (R)-isomer	4.1

THAT, the above oral ED_{50} data clearly indicates that:

(1) NO value is as low as 0.05 mg/kg and

(2) the oral ED_{50} values are consistent with the oral dose range of 10 mg to 1,200 mg.

THAT, it is my opinion that the above data clearly indicates that the statement in MOON:

> The compounds listed below were tested and found to have possible useful antipsychotic activity properties as indicated by their having CNS activity (ED_{50} numbers of less than 50 mg/kg values) in the known hypothermia and/or hypoxic stress tests; (column 9, lines 3-7)

relates to parenteral administration and not oral administration. Hence, there is absolutely NO conflict between the statements:

> In the hypothermia and hypoxic stress tests, compounds of the invention have been found more potent than related compounds, showing $ED_{50's}$ values as low as 0.05 mg/kg.

and

> The compounds also had good activity in the hypothermia test when animals were dosed orally with the drug

and

> Initial dosages of the compounds of the invention are ordinarily in the area of at least 10 mg up to about 1200 mg per day orally.

because the first statement relates to parenteral administration, the second statement provides qualitative information regarding the suitability of the oral route of administration, but offers no guidance for selecting an effective oral dose, and the final statement relates to oral administration and provides specific guidance as to the effective dose. That the inventors had a basis grounded in experimental data for believing that a dose of "at least 10 mg up to about 1200 mg per day orally"

would be effective can be determined (and would have been anticipated) by one of ordinary skill in the art from the oral assay data (Hypothermia assay after oral administration, Table 4, above):

> By making the ordinary assumption that a typical adult human weighs 70 kg, it can be calculated that the minimum observed effective oral dose: 0.23 mg/kg X 70 kg estimated weight of typical adult = 16 mg oral dose
>
> Similar the maximum observed effective dose can be calculated to be as follows (excluding 2 of 23 compounds tested that had activity at 30 mg/kg or greater): 9.7 mg/kg X 70 kg estimated weight of typical adult = 679 mg oral dose

The calculated minimum and maximum observed effective oral doses nearly equal the oral dose range of 10 mg or greater, but less than 1200 mg taught by MOON (column 9, lines 58-61).

(D) Claim 11 of US Patent 5,273,975 (MOON)

THAT, I am aware that MOON discloses the compounds of the invention for "treating central nervous system disorders in animals or human hosts in need thereof" (column 64, lines 64-65).

The method of treating male erectile dysfunction that we claim defines and exemplifies the male erectile dysfunction in a manner that is clearly distinguished by one of ordinary skill in the art from "central nervous system disorders" (MOON). Male erectile dysfunction is defined by three criteria that must be present concurrently. The critieria for Male erectile dysfunction are a condition of persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection; and the disturbance must be marked by distress and interpersonal difficulty; and the effect is not better accounted for by a psychiatric or general medical condition or by the effects of a drug (Diagnostic and Statistical Maual of Mental Disorders, Fourth Edition, (DSM-IV), American Psychiatric Association, Washington, D.C. as well as the DSM-IV Guidebook, American Psychiatric Press, Inc., Washington, D.C., 1995). The diagnostic criteria for Male erectile dysfunction do not require that a central nervous system disorder be present for the diagnosis to be made. Furthermore, the diagnosis of Male erectile dysfunction is specifically excluded by the presence of serious psychiatric disorders (Diagnostic and Statistical Maual of Mental Disorders, Fourth Edition, (DSM-IV), American Psychiatric

Association, Washington, D.C. as well as the DSM-IV Guidebook, American Psychiatric Press, Inc., Washington, D.C., 1995). It is widely believed that Male erectile dysfunction and, indeed other forms of sexual dysfunction, do not result from a central nervous system disorder. The etiology of sexual dysfunction is complex and multifactorials, but cardiovascular, hormonal, and social relationship factors are widely considered to be the primary causal factors (Krane RJ, Goldstein I, De Tejada IS; 1989, Impotence: New Eng. J. Med.321:1648-1659. Spector KR, Boyle M; 1986, The prevalence and perceived aetiology of male sexual problems in a non-clinical sample: Br. J. Med. Psychol. 59:351-358. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB; 1994: Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study: J. Urology 151:54-61. Kaiser FE, Viosca SP, Morley JE, Mooradian AD, Davis SS, Korenman SG; 1988: Impotence and Aging: clinical and hormonal factors. J. Am. Geriatrics Soc. 36:511-519.)

IV. CONCLUSIONS

THAT, even though MOON discloses that the compounds identified therein should be useful for mediating sexual behavior including stimulation of sexual activity and to alleviate impotence, MOON teaches that the operable dosage range should be about 10 to about 1,200 mg. In fact, evidence from human clinical trials and the animal experimentation indicates that the teaching of MOON is in ERROR with regard to sexual function. The human clinical evidence indicates there is a very narrow useful range of about 0.5 to about 5.0 mg; the monkey sexual behavior studies with "142774E" similarly indicates a narrow useful range of about 0.02 to 0.05 mg/kg (equivalent to 1.4 to 3.5 mg administered orally to an adult human).

THAT, it is my opinion, in view of all of the evidence it is most surprising and unexpected that the two compounds of claims 8 and 19 should be useful for treating the four classes of sexual conditions of the above identified patent application;

THAT, it is my opinion that while it appears there is a conflict between the following two statements in MOON:

> That with respect to dosing in humans for the purpose of producing therapeutically beneficial effects "Initial dosages of the compounds of the invention are ordinarily in the area of at least 10 mg up to about 1200 mg per day orally;" (column 9, lines 59-60)

and

In the hypothermia and hypoxic stress tests, compounds of the invention have been found more potent than related compounds, showing ED_{50}'s values as low as 0.05 mg/kg. (column 9, lines 40-43)

in actuality there is absolutely no conflict because they refer to different routes of administration, the former referring to oral administration while the later refers to parenteral administration. In addition, it is clear that MOON's preferred route of administration is oral;

FURTHER, the undersigned declares that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and FURTHER that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of an application or any patent issuing thereon.

Martin D. Meglasson, Date: 12 May 2003

Martin D. Meglasson

Kalamazoo, MI 49001

Appendix 1.

Martin D. Meglasson, Ph.D.

PERSONAL DATA

Home Address: 5337 Whippoorwill Drive
Kalamazoo, MI 49009

Home Telephone: 269-372-2046
Home E-Mail: meglasson@earthlink.net

Business Address: Director
Pharmacology Department
Pharmacia Corporation
301 Henrietta Street
Kalamazoo, MI 49007

Business Telephone: 269-833-1284
Business Fax: 269-833-9763
Business E-Mail: martin.d.meglasson@Pharmacia.com

EDUCATIONAL BACKGROUND

1981-1984 **University of Pennsylvania**
Philadelphia, Pennsylvania
Post-Doctoral Training in Metabolic Diseases (Department of Biochemistry and Biophysics, and Diabetes Research Center; Supervisor: Franz M. Matschinksy, M.D.)

1981 **University of Houston**
Houston, Texas
Ph.D., Endocrinology
Dissertation: Adrenergic Regulation of Insulin and Pancreatic Polypeptide Secretion from Chicken Pancreas

1976 **University of Houston**
Houston, Texas
B.S/M.S., Neurophysiology
Thesis: An Electroencephalographic Study of the Arousal-Sleep Continuum in *Caiman sclerops*

EXECUTIVE EDUCATION

1999 **American Graduate School of International Management**
Glendale, Arizona
Thunderbird/Pharmacia & Upjohn Managing for Growth Program

2000 **Wharton Executive Education, University of Pennsylvania**
Philadelphia, Pennsylvania
Managing People: Power through Influence

Sloan School of Management, Massachusetts Institute of Technology
Cambridge, Massachusetts
Technology and Change in Drug Discovery, Development and the Business of Pharmaceuticals

2001 **Champion Leadership and Team Building ("Leadership Intensives")**
Peapack, New Jersey
Pharmacia Leaders of the Discovery Organization

PROFESSIONAL EXPERIENCE

Academic Appointments:

University of Pennsylvania
Department of Pharmacology
Philadelphia, Pennsylvania

1984-1986 Research Assistant Professor

1986-1989 Assistant Professor

1989-1995 Adjunct Associate Professor

Industrial Employment:

Pharmacia Corp. (formerly The Upjohn Company and Pharmacia & Upjohn)
Kalamazoo, Michigan

1988-1991 Research Scientist

1991-1992 Senior Research Scientist

1992-1996 Senior Scientist

1996-1997 Director, Endocrine Pharmacology and Metabolism

1997-Present Director, Pharmacology

HONORS AND AWARDS

Phi Kappa Phi Honor Society
Beta Beta Beta Honor Society
Solomon A. Berson Research Award for Outstanding Young Investigator,

American Diabetes Association (1984)

Upjohn Laboratories Special Recognition Award (1992)
Upjohn Laboratories Fred Kagan Award for Outstanding Drug Discovery Research (1992)
Upjohn Company VECURE Lectureship (1992)

RESEARCH GRANTS

Research and Development Award, American Diabetes Association, 1984-1986

Metabolic Basis of Fuel Sensing in Pancreatic Beta-Cells, National Institutes of Health, R01 DK35808 (01-03), 1985-1988

Career Development Award, Juvenile Diabetes Foundation, 1986-1989

Glucose-6-Phosphate Metabolism in Pancreatic Beta Cells, The Upjohn Company, 1988-1990

Metabolic Basis of Fuel Sensing in Pancreatic Beta-Cells, National Institutes of Health, R01 DK35808 (04-08), 1988-1993

PROFESSIONAL ORGANIZATIONS

American Diabetes Association
American Society for Biochemistry and Molecular Biology
Endocrine Society
Society for Neuroscience

DRUG CANDIDATES AND OTHER PRODUCTS

Inventor, 13 U.S. Patents (plus foreign equivalents) related to Product Candidates
Responsible Director for Teams producing 2 Product Candidates (Diabetes and Obesity indications)
Principal Scientist and Inventor, U-10483 (Diabetes indication; dropped from Phase 1)
Principal Scientist and Inventor, PNU-106817 (Diabetes indication; dropped from Phase 1)
Inventor, PNU-10483 (Companion Animal indication; dropped from Phase 2)
Principal Scientist and Inventor, PNU-95666E (Sexual Dysfunction indication; dropped from Phase 2 in preference to PNU-142774)
Principal Scientist and Inventor, PNU-142774 (Sexual Dysfunction indication; in Phase 2)

COMMITTEES AND OTHER ACTIVITIES

Pharmacia Committee Memberships:

Anti-Diabetes Lead Finding and Project Team Member
Pioglitazone Development Team Member
Team Leader, Diabetes Strategy Team
Diabetes Program Team Member
U-10483 Development Team Member
Research Library Advisory Committee Member
Responsible Director, Diabetes Program Team
Responsible Director, Inflammation Program Team
Team Leader, Aminoguanidine Team (Sweden)
PNU-91325 Team Member
Protein Tyrosine Phosphatase 1B Team Member
Metabolic Research Review Committee Member (Sweden)
CNS Research Review Committee Member
ID Research Review Committee Member
Trecetilide Core Team Member
PNU-95666E Core Team Member
Animal Health Project 707A Development Team Internal Consultant
Psychiatric Project Team Member
Discovery Management Team Member (Kalamazoo)
Biology Management Team Member (Kalamazoo)
Exploratory Development Committee Member (standing Corporate committee)
Scientist Promotion Committee Member (Kalamazoo)
Responsible Director, Cardiac Ion Channel Committee
Discovery Research Operations Team Member (Kalamazoo)*
CNS Research Leadership Team Member
Southwest Michigan Innovation Center Scientific Advisor
Infectious Diseases Research Therapeutic Area Team *Ad hoc* Member
CNS Research Therapeutic Area Team Member
Elan-Pharmacia Joint Project Team (collaboration governance)*
Urology Strategy Working Group*
CNS Core Team member*
CNS Management Team member*
Infectious Diseases Core Team member*
Infectious Diseases Management Team member*

*, Current committee and project team memberships

University of Pennsylvania Committee Memberships (1984-1988)

Pharmacology Department Faculty Committee Member
Cell Biology Graduate Group Chairperson Search Committee Member
Cell Biology Graduate Group Executive Committee Member
Cell Biology Graduate Group Program Committee Member

Training Activities

Supervision of post-doctoral fellow (Christopher J. de Souza, Ph.D., 1991-1993; current position: Novartis, East Hanover, NJ)

Supervision of post-doctoral fellow (M. Ohta, Ph.D., 1987-1990; current position: University of Osaka, Osaka, Japan)

Lecturer in Pharmacology 100 and Pharmacology 602, University of Pennsylvania School of Medicine (1984-1996)

Grant Reviewer

American Diabetes Association-Michigan Affiliate Scientific Review Committee Member (1991-1993)
Veterans Administration Merit Review Board for Endocrinology (1992-1996)
N.I.H. Physiological Science Study Section *ad hoc* Member (1995-1996)
N.I.H. Metabolism Study Section Member (1994-1997)

Community Service

American Diabetes Association-Michigan Affiliate Board of Directors (1989-1992)

Bronson Methodist Hospital (Kalamazoo, Michigan) Trauma Service Research Advisory Committee (1999-2001)

BIBLIOGRAPHY

In four parts: Regulatory and Development Milestone Documents
Patents
Publications
Internal Summary Reports (confidential Pharmacia work product)

Regulatory and Development Milestone Documents

Compound Evaluation Meeting Summary for PNU-10483, 1991
Pharmacology Section, Investigational New Drug Application for PNU-10483, 1992
Compound Evaluation Meeting Summary for PNU-106817, 1997
Pharmacology Section, Investigational New Drug Application for PNU-106817, 1998
Compound Evaluation Meeting Summary for PNU-91325, 1998
Compound Evaluation Meeting Summary for PNU-95666E Sexual Dysfunction Indication, 1998
Pharmacology Section, Investigational New Drug Application for PNU-95666E, 1999
Compound Evaluation Meeting Summary for PNU-142774, 2000
Pharmacology Section, Investigational New Drug Application for PNU-142774, 2000
Pharmacology Section, Exploratory Development Plan for PNU-95666, 2001
Pharmacology Section, Exploratory Development Plan for PNU-142774, 2001
Response to FDA Contact (4 January 2001) Regarding Abuse Potential for PNU-142774, 2001
Pharmacology Section, Exploratory Development Plan for Intranasal Apomorphine, 2002
Pharmacology Section, Product Development Plan for Intranasal Apomorphine, 2002

Patents

Patents: Total of 81. To access complete listing use hotlink http://gb.espacenet.com/, select "Published Patent Applications Throughout the World" and search "Meglasson" in the inventor field

Issued U.S. Patents:

US6,184,216 Aminoguanidine carboxylate lactams for the treatment of non-insulin- dependent diabetes mellitus.
US6,177,453 Aminoguanidine carboxylate lactams for the treatment of non-insulin- dependent diabetest mellitus.
US6,166,080 Aminoguanidine carboxylates for the treatment of obesity.
US6,008,253 Use of 3-guanidinopropionic acid to increase endurance, stamina and exercise capacity in a mammal.
US5,994,577 Aminoguanidine carboxylates for the treatment of non-insulin- dependent diabetes mellitus.
US5,955,617 Aminoguanidine carboxylate lactams for the treatment of non-insulin- dependent diabetest mellitus.
US5,900,435 Composition, food product and uses of 3-guanidinopropionic acid.
US5,599,841 Use of 3-guanidinopropionic acid in the treatment and prevention of metabolic disorders.
US5,134164 Use of 3-guanidinopropionic acid in the treatment of excess adiposity.
US5,132,324 Use of 3-guanidinopropionic acid in the treatment of non-insulin dependent diabetes mellitus (NIDDM).
US6,274,580 Aminoguanidine carboxylate lactams for the treatment of non-insulin- dependent diabetes mellitus.
US6,329,545 Aminoguanidine carboxylates for the treatment of non-insulin- dependent diabetes mellitus.
US6,455,564 Method of treating sexual disturbances

Publications

Meglasson, M.D., and S.E. Huggins. Sleep in a crocodilian, Caiman sclerops. Comp. Biochem. Physiol. 63A: 561-567, 1979

Meglasson, M.D. Ascorbic acid stimulation of avian pancreatic polypeptide (APP) and insulin release in vitro. Proceedings of the Southwest Section of the Society for Experimental Biology and Medicine 1: 9, 1979

Meglasson, M.D. Perifused chicken pancreas microfragments: regulation of insulin secretion. Proceedings of the Southwest Section of the Society for Experimental Biology and Medicine 2: 8, 1980

Meglasson, M.D., and R.L. Hazelwood. Ascorbic acid diabetogenesis in the domestic fowl. Gen. Comp. Endocrinol. 47: 205-212, 1982

Meglasson, M.D., and R.L. Hazelwood. Adrenergic regulation of avian pancreatic polypeptide in vitro. Am. J. Physiol. 244 (Endocrinol. Metab.): E408-E413, 1983

Meglasson, M.D., P.T. Burch, D.K. Berner, H. Najafi, A.P. Vogin, and F.M. Matschinsky. Chromatographic resolution and kinetic characterization of glucokinase from islets of Langerhans. Proc. Natl. Acad. Sci. USA 80: 85-89, 1983

Meglasson, M.D., P.T. Burch, M. Hoenig, W.L. Chick, and F.M. Matschinsky. Identification and significance of glucokinase in transplantable insulinomas. J. Biol. Chem. 258: 2094-2097, 1983

Meglasson, M.D., and F.M. Matschinsky. Discrimination of glucose anomers by glucokinase from liver and transplantable insulinoma. J. Biol. Chem. 258: 6705-6708, 1983

Meglasson, M.D., M.A. Schinco, and F.M. Matschinsky. Mannose phosphorylation by glucokinase from liver and transplantable insulinoma: cooperativity and discrimination of anomers. Diabetes 32: 1146-1151, 1983

Matschinsky, F.M., M.D. Meglasson, P.T. Burch, D.K. Berner, H. Najafi, A.P. Vogin, D. Garfinkel, and Garfinkel, L. Glucokinase (ATP: D-glucose 6-phosphotransferase, EC 2.7.1.2), the glucose sensor of pancreatic islet β-cells. In: Diabetes 1982. E.N. Mngola, ed., Excerpta Medica (Amsterdam), pp. 337-344, 1983

Meglasson, M.D., and F.M. Matschinsky. Relative specificity of glucokinase for glucose anomers. Diabetes 32 (Suppl. 1): 8A, 1983

Matschinsky, F.M., M.D. **Meglasson**, and M.A. Schinco. Discrimination of glucose and mannose anomers by glucokinase from liver and transplantable insulinoma. Diabetologia 25: 179-180, 1983

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Cellular Membrane Systems. Woudschoten, Zeist, The Netherlands, 1983

Meglasson, M.D., and Matschinsky, F.M. Purification of the putative islet cell glucose sensor glucokinase from isolated pancreatic islets and insulinoma tissue. In: Methods in Diabetes Research, Volume 1: Laboratory Methods, Part A. J. Larner and S.L. Pohl, Eds. New York: Wiley. pp. 213-226, 1984

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Garfinkel, D., L. Garfinkel, M.D. **Meglasson**, and F.M. Matschinsky. Computer modeling identifies glucokinase as glucose sensor of pancreatic β-cells. Am. J. Physiol. 24: R527-R536, 1984

Meglasson, M.D., and R.L. Hazelwood. Adrenergic regulation of insulin secretion from the chicken pancreas in vitro. Gen. Comp. Endocrinol. 56: 82-89, 1984

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